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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/507,968	02/22/2000	Guo-Liang Yu	PF343P3	2764

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/31/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/507,968	YU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28, 31-41, 44-45, 48-81, 83-213, 215-223, 225-238, 240-341, and 343-429* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26-28,31-34,36-38,124,125,134-137,139-143,152-155 and 157-159* is/are allowable.

6)☒ Claim(s) *35, 39-41, 44-45, 48-81, 83-123, 126-133, 138, 144-151, 156, 160-213, 215-223, 225-238, 240-341, and 343-429* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647, Examiner Bridget E. Bunner.

Status of Application, Amendments and/or Claims

The amendment of 03 May 2002 (Paper No. 14) has been entered in full. Claims 26, 39, 57, 78, 103, 160, 178, 196, 213, 225, 232-238, 240, 247, 268, 273, 290, 307, 324, and 341 are amended. Claims 1-25, 29-30, 42-43, 46-47, 82, 214, 224, 239, and 342 are cancelled. Claims 360-429 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 26-28, 31-41, 44-45, 48-81, 83-213, 215-223, 225-238, 240-341, and 343-429 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection of originally filed claims 26-359 under 35 U.S.C. § 112, first paragraph as set forth at pg 3-8 of the previous Office Action (Paper No. 11, 06 November 2001) is *withdrawn in part* in view of the amended claims (Paper No. 14, 03 May 2002). Please see section on 35 U.S.C. § 112, first paragraph, below.

2. The rejection of originally filed claims 26-359 under 35 U.S.C. § 102(e) as set forth at pg 11-12 of the previous Office Action (Paper No. 11, 06 November 2001) is *withdrawn* in view of Applicant's persuasive arguments (Paper No. 14, 03 May 2002).

3. The rejection of originally filed claims 247-359 under 35 U.S.C. § 112, first paragraph (written description for deposited biological material) as set forth at pg 10-11 of the previous

Office Action (Paper No. 11, 06 November 2001) is *withdrawn* in view of the statement by Applicant's representative (Paper No. 14, 03 May 2002).

4. It is noted to Applicant that the formal drawings submitted were received by the Office on 14 August 2001 (Paper No. 10).

Information Disclosure Statement

5. The information disclosure statement filed 03 May 2002 (Paper No. 15) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Objections

6. Claims 215 and 343 are objected to because of the following informalities:

Claims 215 and 343 depend from claims 214 and 342, which are currently withdrawn.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. Claims 35, 39-41, 44-45, 48-81, 83-123, 126-133, 138, 144-151, 156, 160-213, 215-223, 225-238, 240-341, and 343-429 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) an isolated protein comprising an amino acid sequence that is 90% or 95% or more identical to an amino acid sequence selected from the group consisting of : (a) the amino acid sequence of amino acid residues 1 to 285 of SEQ ID NO: 2; and (b) the amino acid sequence of amino acid residues 73-285 of SEQ ID NO:2; wherein said protein induces B cell proliferation and differentiation, and (ii) any isolated protein comprising

at least an amino acid sequence that consists of amino acids 134-285 of SEQ ID NO: 2, wherein said protein induces B cell proliferation and differentiation, does not reasonably provide enablement for all the protein derivatives and fragments as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for originally filed claims 26-359 at pg 3-8 of the previous Office Action (Paper No. 11, 06 November 2001).

Applicant's arguments (Paper No. 14, 03 May 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts the pending claims are fully enabled. Applicant argues that one skilled in the art, enlightened by the disclosure of the specification, could routinely make the claimed polypeptides and use the polypeptides, for example, to treat or diagnose an autoimmune disease or an immunodeficiency.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that neutrokine-alpha (SEQ ID NO: 2) is a 285 amino acid protein that is designated as a B lymphocyte stimulator based on its biological activity (pg 325, [0842]). The specification also discloses that expression of neutrokine-alpha cDNA in mammalian cells and insect cells identify a 152 amino acid soluble form with an N-terminal sequence beginning with the alanine residue at amino acid 134 (pg 326, [0842]). The specification teaches that recombinant neutrokine-alpha induces a dose-dependent proliferation of tonsillar B cells (pg 327, [0846], Figure 9A-9B). Furthermore, the specification teaches that lineage-specific analyses of whole human peripheral blood cells indicate that binding of

biotinylated neutrokine-alpha is undetectable on T cells, monocytes, NK cells, and granulocytes. Biotinylated neutrokine-alpha was found to bind peripheral CD20+ B cells, as well as B cell tumor lines (pg 327, [0846]). The specification teaches that "taken together, these results confirm that neutrokine-alpha displays a clear B cell tropism in both its receptor distribution and biological activity" (pg 327, [0846] lines 14-15). The specification also discloses that flow cytometric analysis of spleens from mice treated with neutrokine-alpha indicate that neutrokine alpha increased the proportion of mature B cells about 10-fold over that observed in control mice (pg 329, [0850], Figure 11B-11C, Table IV).

However, the specification does not teach any functional or structural characteristics of fragments, derivatives, or variants of the neutrokine-alpha polypeptide of SEQ ID NO: 2, other than polypeptides comprising amino acids 73-285 or amino acids 134-285 of SEQ ID NO: 2. The specification does not teach any methods or working examples that indicate polypeptide variants that do not contain amino acids 134-285 of SEQ ID NO: 2 have any function. For example, the specification does not teach that a protein comprising amino acid residues 271-278 of SEQ ID NO: 2 has any function. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also

be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, Applicant has amended the originally filed claims and added claims to recite the limitation that the neutrokine-alpha protein "modulates leukocyte proliferation, differentiation or survival". However as discussed above, the specification teaches that

neutrokine-alpha induces B cell proliferation and differentiation and displays a clear B cell tropism in both its receptor distribution and biological activity (pg 327-329). The specification does not teach that neutrokine-alpha increases/decreases the proliferation, differentiation, or survival of all possible leukocyte cells. Relevant literature teaches that four main groups comprise the class of mononuclear leukocytes: B lymphocytes, T lymphocytes, macrophages, and NK cells (Elgert, K. Immunology: Understanding the Immune System. Wiley-Liss: New York, 1996, pg 24.). The specification of the instant application clearly indicates that biotinylated neutrokine-alpha is undetectable on T cells, monocytes, NK cells, and granulocytes and that neutrokine alpha stimulates the proliferation and differentiation of B cells (pg 327, [0846] through pg 329). Therefore, one skilled in the art would not be able to predict that neutrokine-alpha would be able to increase or decrease the proliferation or differentiation of any leukocyte cells, other than B cells. The specification also does not teach that neutrokine-alpha affects the survival of any leukocytes, including B cells. Additionally, it is noted that the specification does not teach that neutrokine-alpha is cytotoxic to neutrokine-alpha receptor bearing cells. The examples in the specification utilizing B cells are not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to determine if neutrokine-alpha increases, decreases, or does not affect the proliferation, differentiation, and survival of T lymphocytes, macrophages, and NK cells. Such trial and error experimentation is considered undue.

Finally, the specification of the instant application does not teach any methods or working examples that generate a neutrokine-alpha protein multimer. There is no guidance in

the specification teaching one skilled in the art how to create a neutrokine-alpha multimer and undue experimentation would be required of the skilled artisan to do so. For example, what methods would be used to link the proteins? How many would be linked? What would be the amino acid sequences of each protein that make up the multimer? Would each neutrokine-alpha amino acid sequence used to make up the multimer be different or the same? What structural and functional characteristics would these multimers have?

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims that do not *entirely* contain amino acid residues 134-285 of SEQ ID NO: 2 and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite specific structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 57-60, 62-81, 83, 87-104, 108-123, 126-133, 138, 144-151, 156, 160-213, 215-223, 225-232, 234-238, 240-272, 274, 276-341, and 343-429 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is

set forth for originally filed claims 26-359 at pg 8-10 of the previous Office Action (06 November 2001, Paper No. 11).

The claims are directed to neutrokine-alpha variants, derivatives, fragments, and fusion proteins that do not *entirely* contain amino acid residues 134-285 of SEQ ID NO: 2.

Applicant's arguments (Paper No. 14, 03 May 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts at pg 17 of the Response (03 May 2002, Paper No. 14) that one skilled in the art would reasonably conclude that Applicant had possession of the claimed polypeptides on the filing date of the present application and the filing date of the earliest priority document to which the present application claims priority. Applicant also contends that one skilled in the art could readily envision or recognize a representative number of members of the claimed genre based upon the teachings of the specification, and thus, could reasonably conclude that the inventors had possession of the claimed invention in the specification as filed.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application teaches that neutrokine-alpha (SEQ ID NO: 2) is a 285 amino acid protein (pg 325, [0842]). The specification also discloses that expression of neutrokine-alpha cDNA in mammalian cells and insect cells identify a 152 amino acid soluble form with an N-terminal sequence beginning with the alanine residue at amino acid 134 (pg 326, [0842]). However, the specification does not teach any polypeptide variants or their structural or functional characteristics wherein the polypeptide variants exclude any amino acid residues of the soluble protein (amino acids 134-285 of SEQ ID NO: 2). The description of one neutrokine-alpha polypeptide species (SEQ ID NO: 2), particularly amino acids 134-285 of SEQ ID NO: 2,

is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and fragments of the neutrokine-alpha protein of SEQ ID NO: 2.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The protein itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated protein comprising at least an amino acid sequence that consists of amino acids 134-285 of SEQ ID NO: 2, wherein said protein induces B cell proliferation and differentiation, but not the full breadth of the claim meets the written

description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 39-41, 44-45, 48-81, 83-123, 126-127, 130-131, 144-145, 148-149, 160-213, 215-223, 247-272, 274-275, 278-279, 290-342, 343-429 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "modulates" in claims 39-41, 44-45, 48-81, 83-123, 126-127, 130-131, 144-145, 148-149, 160-213, 215-223, 247-272, 274-275, 278-279, 290-342, 343-429 is a relative term which renders the claim indefinite. The term "modulates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It cannot be determined if "modulates" means, for example, "increases" or "decreases".

Allowable Subject Matter

Claims 26-28, 31-34, 36-38, 124-125, 134-137, 139-143, 152-155, and 157-159 are allowable.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
January 10, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER